Deep Brain Stimulation in Psychiatry

Mechanisms, Models, and Next-Generation Therapies

Mustafa Taha Bilge, PhD[a], Aishwarya K. Gosai, BA[a], Alik S. Widge, MD, PhD[a,b,*]

KEYWORDS

• Closed-loop DBS • Network-oriented DBS • DBS in psychiatry
• Mechanisms of DBS • Dimension-oriented psychiatry

KEY POINTS

- The likely mechanism of deep brain stimulation is altered interneuronal communication, which may include alterations in neural firing patterns, oscillatory dynamics, or synaptic plasticity.
- Deep brain stimulation acts at the network level, not on single brain structures.
- Advanced technologies, including closed loop systems, are being deployed in movement disorders. Recent progress in novel applications suggests that they may soon be used in psychiatry.
- The optimal use of deep brain stimulation likely requires a dimensional approach to identify patients with treatment-amenable brain circuit impairment.

Disclosure Statement: A.S. Widge receives consulting income and device donations from Medtronic, which manufactures deep brain stimulation systems. A.S. Widge has also filed multiple patent applications related to closed loop deep brain stimulation, none of which is yet commercially licensed.
Preparation of this work was not sponsored or supported by any commercial entity. A.S. Widge, A.K. Gosai, and M.T. Bilge were supported by grants to A.S. Widge from the Brain & Behavior Research Foundation, National Institutes of Health (MH109722, MH111320, and NS100548), and Defense Advanced Research Projects Agency (Cooperative Agreement W911NF-14-2-0045). The views, opinions, and/or findings expressed are those of the authors and should not be interpreted as representing the official views or policies of any sponsor or funding source.
[a] Department of Psychiatry, Massachusetts General Hospital, Harvard Medical School, 149 13th Street, Charlestown, Boston, MA 02129, USA; [b] Picower Institute for Learning and Memory, Massachusetts Institute of Technology, Cambridge, MA, USA
* Corresponding author. Department of Psychiatry, Massachusetts General Hospital, Harvard Medical School, 149 13th Street, Room 2627, Charlestown, MA 02129.
E-mail address: awidge@partners.org

Psychiatr Clin N Am ■ (2018) ■–■
https://doi.org/10.1016/j.psc.2018.04.003 **psych.theclinics.com**

Abbreviations	
CBF	Cerebral blood flow
LFP	Local field potential
MDD	Major depression
NAc	Nucleus accumbens
OCD	Obsessive-compulsive disorder
PR	Parkinson disease
STN	Subthalamic nucleus

INTRODUCTION: THE PROMISE AND FRUSTRATIONS OF DEEP BRAIN STIMULATION IN PSYCHIATRY

As discussed in the companion article by Darin D. Dougherty, "Deep Brain Stimulation—Clinical Applications," in this issue, deep brain stimulation (DBS) has promise in intractable obsessive-compulsive disorder (OCD) and major depression (MDD), but has not fared well in traditional randomized trials. This contrasts with the success of DBS in Parkinson disease (PD), where it has become a part of standard care.[1] The difference in outcomes arises because PD and other movement disorders arise from well-explored neural circuitry, with well-understood, reliable measures of symptoms. Psychiatric conditions arise from multiple dysfunctional neural circuits, not all of which are known or well-described.[2,3] Our symptom measures are also less robust, diluting the clinical signal.[4,5] For example, a metaanalysis of depression questionnaires showed that general factors, such as mood, explain more variance than any specific MDD symptom.[6] In the *Diagnostic and Statistical Manual of Mental Disorders, 5th edition*, field trials, comorbidity was more common than "pure" diagnoses, suggesting that diagnostic criteria and rating scales do not measure separable entities.[7]

Studies in both psychiatric and PD patients have yielded proposed mechanisms of DBS, leading to new treatment strategies. Some of these proposals emphasize anatomy; others have both functional and anatomic components. We argue that DBS in psychiatry depends on both function and anatomy, viewed at the circuit/network level. Herein, we review the functional and network-oriented theories of psychiatric DBS. We begin each section with a review of what is known or strongly suspected, then highlight directions the field may soon take.

NEUROPHYSIOLOGIC MECHANISMS OF DEEP BRAIN STIMULATION

Neural Inhibition

DBS often mimics the clinical effect of a brain lesion at the target site. Most of the PD and MDD/OCD targets were chosen because a lesion at that target was known or expected to ameliorate disease.[8,9] Several studies reported decreased neural activity at the DBS site.[10–12] Yet, DBS-like stimulation can also increase neural activity, depending on how the electric field is oriented relative to individual cells.[13,14] DBS also seems to increase brain metabolism at structures connected to the target.[15–17] This finding casts doubt on the inhibition hypothesis.

Informational Lesion

One possible explanation for these contradictions is that DBS may be inhibitory at the level of information flow. The high-frequency pulses (>100 Hz) used in DBS are above the firing frequency of most neurons, meaning that DBS effectively "takes over" the